REMARKS

Claims 1-13 and 15-18 remain pending in this application.

The present claims relate, in part, to a method for making a diagnosis of ulcerative colitis caused by *Fusobacterium varium* in a patient, which comprises:

(a) obtaining sera from said patient;

(b) detecting an antibody specific for *Fusobacterium varium* in said sera; and

(c) correlating the presence of an antibody specific for *Fusobacterium varium* in said sera with ulcerative colitis (see Claim 16).

The inventors have discovered that the present method is particularly good for the differential diagnosis of ulcerative colitis.

The rejection of Claims 16-18 under 35 U.S.C. §112, first paragraph, is respectfully traversed.

In the Official Action, the position is taken that "The specification fails to teach how a sample is obtained? How to determine the amount of antibody significant to make a diagnosis of ulcerative colitis? How to assure that the target antibody (i.e., *Fusobacterium varium*) is obtained and not a mixture of antibodies from other colonic bacteria? Nor does the specification provide a correlation between how to diagnosis of ulcerative colitis and the detection of *Fusobacterium varium* antibodies." (see paper number 10, page 5, lines 1-6).

Applicants note that Claim 16 has been amended to specifically indicate that the classification of ulcerative colitis sought to be diagnosed is "ulcerative colitis caused by *Fusobacterium varium*." Accordingly, the question posed by the Examiner of how to assure

that the target antibody (i.e., *Fusobacterium varium*) is obtained and not a mixture of antibodies from other colonic bacteria has been rendered moot.

The Examiner has defined the relative skill in the art to be "post-doctoral level" (see paper number 10, page 5, line 20). Applicants submit that with such a high level of skill, the skilled artisan could easily carry out the method of Claim 16 by using either a western blotting method or an enzyme-linked immunosorbent assay (ELISA) with the present specification in hand. Specific reference is given to Example 1 (page 8, line 24 to page 9, line 15), which clearly shows that *Fusobacterium varium* can be readily isolated and an antibody specific thereto can be obtained. Moreover, the alleged deficiencies in the specification, highlighted above, would be well within the purview of routine experimentation by the skilled artisan.

In order to further demonstrate the operability of the present invention, Applicants submit herewith a copy of Ohkusa et al in which the Applicants have established an clear indication of a causal relationship between *Fusobacterium varium* and ulcerative colitis (see Abstract). Further, Ohkusa et al demonstrate a proof of principal and in so doing support the inventive method for making a diagnosis of ulcerative colitis caused by *Fusobacterium varium* in a patient, which comprises:

(a) obtaining sera from said patient;

(b) detecting an antibody specific for *Fusobacterium varium* in said sera; and

(c) correlating the presence of an antibody specific for *Fusobacterium varium* in said sera with ulcerative colitis.

Specifically, Ohkusa et al demonstrate that only sera from patients with ulcerative colitis gave specific reactions with *Fusobacterium varium* in Western blot assays from a collection of patients suffering from active ulcerative colitis, Crohn's disease, ischemic

colitis, and colon adenomas (see Abstract and Results). With *Fusobacterium varium* antigens, bands for IgG, IgA, and IgM were seen at 30-83 kDa (see Figure 1, page 851). Strong signals were evident at 70 and 48 kDa with sera from 61% of the patients with active UC, 13% with Crohn's disease, and 29% of the healthy controls (see Results, page 850, second column). Further, only antigens from *Fusobacterium varium* bacterial species gave specific bands of reactivity (see Results, page 850, second column).

Further, Ohkusa et al demonstrate that the combination of IgG, IgA, and IgM, as well as either IgG or IgA alone, gave higher mean OD for patients with active ulcerative colitis (0.716, 0.405, and 0.091, respectively) than for Crohn's disease (0.117, 0.066, and 0.033, respectively; $P<0.001$) or healthy controls (0.108, 0.060, and 0.036, respectively; $P<0.001$) (see Results, bridging pages 850-851).

Moreover, Ohkusa et al demonstrate that *Fusobacterium varium* was detected immunohistochemically in the exudates, surface mucus, and crypts of the colonic mucosa in 84% of the patients with active ulcerative colitis (see Figure 3, page 851). In contrast, only 13% of the patients in remission for ulcerative colitis, 16% of patients with Crohn's disease, 13% of patients with ischemic colitis, and 3% of patients with colon adenoma gave positive immunostaining reactions (see Results, bridging pages 851-852). The antibody was determined to be specific for *Fusobacterium varium* (see Results, bridging pages 851-852).

MPEP §2164.04 states:

> "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

At page 8, line 24 to page 9, line 15, Applicants provide an explicit example showing that *Fusobacterium varium* can be readily isolated and an antibody specific thereto can be obtained. On page 5, lines 5-18, Applicants provide a detailed explanation of how to use the information garnered from this Example in diagnosing patients suffering from ulcerative colitis by determination of serum antibody titers.

In the Office Action, the Examiner has maintained the enablement rejection. The basis for this rejection appears on pages 3-8 of the Office Action (paper number 21). Specifically, the Examiner notes that the etiology of ulcerative colitis is unknown and that the artisan cannot conclude that the detection of *F. varium* is a viable diagnostic marker. The Examiner cites Coleman et al to support the proposition that *F. varium* is present in the human gastrointestinal tract of healthy individuals. However, Applicants note that Coleman et al does not relate to an antibody response to *F. varium* and therefore it is unclear how this reference directly relates to the present invention. More specifically, it is unclear how Coleman et al necessarily refutes the claimed correlation of the presence of an antibody specific for *Fusobacterium varium* in said sera with ulcerative colitis.

In the outstanding Office Action, the Examiner states that Coleman et al is merely cited to evidence that *Fusobacterium varium* is one of six microbial competitors that reside in the gastrointestinal tract. The Examiner further asserts that although Ohkusa et al establish a relationship between *Fusobacterium varium* and ulcerative colitis, this reference and the specification fail to establish that *Fusobacterium varium* is **the** causative agent of ulcerative colitis. Be that as it may, Applicants note that the claimed invention does not exclude the possibility that alternative causative agents exist. The claimed invention is concerned with diagnosing (i.e., identifying) ulcerative colitis caused by *Fusobacterium varium.* In other

words, the claimed invention is only concerned with identifying patients in whom detection of *Fusobacterium varium* in sera is indicative of ulcerative colitis.

Further evidence of the intimate relationship between *Fusobacterium varium* and ulcerative colitis is proffered by Ohkusa et al (Gut 2003; 52: 79-83), a copy of which is **enclosed herewith**. In this paper, Ohkusa et al (2003) isolated bacteria from ulcerative colitis patients and tested the same for cytotoxicity to Vero cells and to determine whether the toxin induces ulcerative colitis-like lesions in animals (see Abstract). As evidenced by Table 1 on page 80, of the 20 species obtained from 42 isolates only *Fusobacterium varium* proved to be cytotoxic to Vero cells. This study also reports that culture supernatants of *Fusobacterium varium* contained high concentrations of n-butyric acid, which was also cytotoxic to Vero cells. Moreover, 24 hours after mice were given enemas containing butyric acid or *Fusobacterium varium* culture supernatants, colonic ulcers with crypt abscesses, inflammatory cell infiltration, and apoptotic changes were observed (see Results, pages 81-82 and Figure 3 on page 82).

Accordingly, contrary to the assertions by the Examiner, the presence of *Fusobacterium varium* in sera may be used as a diagnostic marker of ulcerative colitis. As such, as evidenced by the present application coupled with Ohkusa et al (2002), Ohkusa et al (2003), and the knowledge generally available in the art, a person possessing a post-doctoral level of experience may perform the claimed invention and readily appreciate the applicability of the results obtained thereby without undue experimentation.

In view of the foregoing, Applicants submit that the present invention is enabled as defined by 35 U.S.C. §112, first paragraph. Accordingly, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 16-18 under 35 U.S.C. §112, second paragraph, is traversed in part and obviated in part by appropriate amendment.

The Examiner has indicated that this ground of rejection is rejected for failing to recites essential steps, including: "1) providing a sample..., 2) determining that the target antibody... is obtained and not antibodies to a mixture of colonic bacteria, 3) determining the amount of antibody significant to make a diagnosis and 4) the correlation as to how to diagnose..." (see paper number 10, page 2, numbered paragraph 4).

Applicants disagree with the Examiner with respect to the omission of essential steps. MPEP §2171 defines definiteness as "whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art." In the present application, the Examiner has defined the relative skill in the art to be "post-doctoral level" (see paper number 10, page 5, line 20). As such, the skilled artisan possessing such a high level of skill would recognize the full scope of the claims. In particular, the skilled artisan would appreciate, without further amendment, how to make a diagnosis of ulcerative colitis caused by *Fusobacterium varium* in a patient, which comprises:

(a) obtaining sera from said patient;

(b) detecting an antibody specific for *Fusobacterium varium* in said sera; and

(c) correlating the presence of an antibody specific for *Fusobacterium varium* in said sera with ulcerative colitis (see Claim 16).

The ability of the artisan to practice the claimed invention is directly related to the fact that the alleged omitted steps *are* embraced by the claims as presented. Specifically, alleged omitted steps 1) – 3) are inherently embraced by the step for detecting an antibody specific for *Fusobacterium varium* in said sera. For example, these alleged omitted steps are related to the detection technique as further defined in Claims 17-18. The skilled artisan having "post-

doctoral level" skill would readily appreciate preparation steps (i.e., 1) providing a sample..., 2) determining that the target antibody... is obtained and not antibodies to a mixture of colonic bacteria) and the detection limits (i.e., 3) determining the amount of antibody significant to make a diagnosis) associated with Western blotting and/or ELISA methods.

The Examiner has maintained this ground of rejection stating: "how were the ELISA and Western blotting methods used, were whole *Fusobacterium vairum* organisms used to detect antibodies or were proteins of *F. varium* (antigens) used in the assay (paper number 17, page 3, line13-15). Applicants again submit that with the specification in hand, as represented by the disclosure at page 9, the artisan would readily appreciate the scope of present Claims 16-18, as well as the techniques embraced by Western blotting and/or ELISA methods. Applicants note that the Examiner has offered now evidence and/or explanation to refute their argument. The Examiner merely concludes "It is the Examiner's position that claims 16-18 are indefinite and do not meet the requirement of 35 U.S.C. 112, second paragraph." However, Applicants wonder how this *opinion* by the Examiner can usurp the understanding and appreciation of the invention by a person possessing the level of skill in the art that the office has determined to be "post-doctoral level."

In view of the foregoing, Applicants believe that the language of the claims are such that a person of ordinary skill in the art could interpret the metes and bound of the claims so as to understand how to avoid infringement (MPEP §2173.02). Applicants note that this rejection appears to be, at best, because the Examiner merely wants the Applicant to improve the clarity or precision of the language used. However, since the skilled artisan can readily appreciate the meaning of the claims, Applicants submit that further amendments are unnecessary. Therefore, Applicants request withdrawal of the claim rejection pursuant to MPEP §2173.02.

For the foregoing reasons, Applicants submit that Claims 16-18 are in compliance with 35 U.S.C. §112, second paragraph. Withdrawal of this ground of rejection is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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